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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT
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INVENTOR(S)/APPLICANT(S).			
LAST NAME	FIRST NAME	MI	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY
EISENBACH-SCHWARTZ	Michal		Rehovot, Israel
YOLES	Ester		D.N. Nahal Soreq, Israel

[ ] Additional inventors are being named on separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

VACCINE AND METHOD FOR TREATMENT OF HUNTINGTON'S DISEASE

CORRESPONDENCE ADDRESS

Direct all correspondence to the address associated with **Customer Number 001444**, which is presently:

BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W., Suite 300
Washington, D.C. 20001-5303

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Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.

By: _____
Roger L. Browdy
Registration No.: 25,618

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RLB:gsk

PRON-028 US PROV

VACCINE AND METHOD FOR TREATMENT OF HUNTINGTON'S DISEASE

Inventors: Michal SCHWARTZ and Ester YOLES

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to compositions, e.g. vaccines, and methods for the treatment of Huntington's disease.

Huntington's Disease

Huntington's disease (HD), identified in the late 1800s by the physician George Huntington, is an autosomal dominant neurodegenerative disease whose symptoms are caused by the loss of cells in the basal ganglia of the brain. This damage to cells affects cognitive ability (thinking, judgment, memory), movement, and emotional control. HD is characterized by uncontrollable, dancelike movements and personality changes. HD patients develop slurred speech, an unsteady walk and difficulty in swallowing. There is no effective treatment for HD. After a long illness, individuals with HD die from complications such as choking or infection.

In 1993, the mutation that causes HD was identified as an unstable expansion of CAG repeats in the *IT15* gene encoding huntingtin, a protein of unknown function (Menalled and Chesselet, 2002). The CAG repeat expansion results in an increased stretch of glutamines in the N-terminal portion of the protein, which is widely expressed in brain and peripheral tissues (Gutekunst *et al.*, 1995). The exact mechanisms underlying neuronal death in Huntington's disease remain unknown. Proposed mechanisms have included activation of caspases or other triggers of apoptosis, mitochondrial or metabolic toxicity, and interference with gene transcription. Recent advances in the understanding of the pathophysiology of

neurodegenerative diseases in general and of Huntington's disease in particular, have suggested new therapeutic strategies aimed at slowing progression or delay onset of the neurodegenerative disease.

5 Pathological disorders of the central nervous system (CNS)

Acute and/or chronic neuronal loss in the adult CNS results in the irreversible loss of function due to the very poor ability of mature nerve cells to proliferate and compensate for the lost neurons. Thus attenuating or reducing neuronal loss is essential for preservation of function. In most of the neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and Huntington's disease, the etiology is not clear, hence they are incurable. Nevertheless, there are some primary and secondary risk factors which are the target for therapeutic intervention aiming at inhibiting or attenuating progress of neuronal loss, collectively termed as neuroprotective therapy. Some of the risk factors are disease-specific but others, like excitatory amino acids, free radicals and nitric oxide, are common to all the neurodegenerative disorders. These factors are essential self components in the healthy CNS, but with their accumulation in excess amounts in the degenerative tissue, they become cytotoxic leading to the spread of damage beyond the initial cause of neuron death.

Glutamate is one of the most common mediators of toxicity in acute and chronic degenerative disorders like status epilepticus, cerebral ischemia, traumatic brain injury, ALS, Huntington's disease, lathyrisms and Alzheimer's disease. Glutamate is a primary excitatory neurotransmitter in the human CNS. L-glutamate is present at a majority of synapses and is capable of displaying dual activity: it plays a pivotal role in normal functioning as an essential neurotransmitter, but becomes toxic when its physiological levels are exceeded.

In order to minimize neuronal loss (neuroprotection) several approaches have been adopted, at which the most common is targeting the risk factors in an attempt to neutralize or inhibit their action. Unfortunately, these therapeutic strategies showed marginal efficacy in human subjects with concomitant severe side effects.

The failure of agents with discrete singular mechanisms of action argues for a multi-pronged approach.

The present inventors are following a fundamentally different approach to nerve presentation and restoration, taking advantage of natural physiological mechanisms of protection and self-healing. The immune system is the body's natural system for tissue healing and repair. Yet, since the CNS is an immune privileged site, it has often been assumed that immune activity would have a negative impact on healing of the CNS after injury. Discoveries of the inventor Prof. Michal Schwartz and her colleagues have challenged this assumption with a new concept according to which the immune system has the capacity to protect the CNS from the self-destructive compounds that cause nerve degeneration. In extensive in vitro and in vivo studies, Prof. Schwartz has shown that an appropriately-controlled boost to the immune response protects CNS cells from further degeneration by causing immune cells to recognize the lesion site, home there, and protect CNS cells.

The concept of T cell-dependent "protective autoimmunity" has been formulated by the inventor Prof. Michal Schwartz and her group (Hauben & Schwartz, 2002; Kipnis & Schwartz, 2002; Schwartz & Kipnis, 2001; Schwartz et al., 1999). According to this concept, an acute or chronic insult to the CNS triggers an autoimmune response directed against proteins residing in the lesion site. T cells homing to the lesion site are activated by cells presenting the relevant antigen. Once activated, they augment and control local immune cells, allowing efficient removal of toxic compounds and tissue debris, thus protecting the damaged nerves from further degeneration. The potential of the immune system to counteract the hostile conditions is enhanced by boosting the normal immune response. Based on this hypothesis, boosting the immune system with a suitable antigen should provide neuroprotection. Among suitable antigens identified by the present inventors is Copolymer 1.

Copolymer 1 (Cop 1 or Glatiramer) is a random non-pathogenic synthetic copolymer composed of the four amino acids, L-tyrosine, L-glutamate, L-lysine and

L-alanine. Glatiramer acetate has been approved in several countries for the treatment of multiple sclerosis under the trademark Copaxone® (a trademark of Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel).

Vaccination with Cop 1 or with Cop 1-activated T cells have been shown by the present inventors to boost the protective autoimmunity, after traumatic CNS insult, thereby reducing further injury-induced damage, and can further protect CNS cells from glutamate toxicity. Reference is made to our previous United States Patent Application Serial Nos. 09/756,301 and 09/765,644, both dated 22 January, 2001, herein incorporated by reference in their entirety as if fully disclosed herein, corresponding to WO 01/93893, which disclose that Cop 1, Cop 1-related peptides and polypeptides and T cells activated therewith protect CNS cells from glutamate toxicity (USSN 09/756,301) and prevent or inhibit neuronal degeneration or promote nerve regeneration in the CNS or PNS (USSN 09/765,644; WO 01/52878).

Prof. Schwartz and colleagues have shown that Cop 1 acts as a low-affinity antigen that activates a wide range of self-reacting T cells, resulting in neuroprotective autoimmunity that is effective against both CNS white matter and grey matter degeneration (Schwartz and Kipnis, 2002). Schwartz and Kipnis, 2002). The neuroprotective effect of Cop 1 vaccination was demonstrated by the inventors in animal models of acute and chronic neurological disorders such as optic nerve injury (Kipnis *et al.*, 2000), head trauma (Kipnis et al., 2003), glaucoma (Schori *et al.*, 2001), amyotrophic lateral sclerosis (Angelov et al., 2003) and in the applicant's patent applications WO 01/52878, WO 01/93893 and WO 03/047500.

SUMMARY OF THE INVENTION

It has now been found, in accordance with the present invention, that treatment, e.g. immunization with Cop 1 can protect HD R6/2 transgenic mice overexpressing a mutated human gene encoding huntingtin, a model for Hungtinton's disease, from neuron degeneration.

The present invention thus relates, in one aspect, to a method for treatment of a patient suffering from Huntington's disease, which comprises administering to said patient a therapeutically active amount of an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide.

In one embodiment, the invention relates to a method for reducing disease progression, and/or protection from neurodegeneration and/or protection from glutamate toxicity in a patient suffering from Huntington's disease, which comprises administering to said patient a therapeutically active amount of an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide.

In another embodiment, the invention relates to a method for reducing disease progression, and/or protection from neurodegeneration and/or protection from glutamate toxicity in a patient suffering from Huntington's disease, which comprises immunizing said patient with an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide.

In another aspect, the present invention provides a pharmaceutical composition for treatment of Huntington's disease comprising a pharmaceutically acceptable carrier and an active agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide. In one embodiment, said pharmaceutical composition is a vaccine.

In a further aspect, the present invention relates to the use of an active agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide, for the manufacture of a pharmaceutical composition for for treatment of Huntington's disease. In one embodiment, said pharmaceutical composition is a vaccine.

In the most preferred embodiment, the agent is Copolymer 1 and the composition is administered once every 4-6 weeks, preferably every 6 weeks.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 shows the neuroprotective effect on retinal ganglion cells (RGCs) of mice by immunization with different doses of Cop 1 (25, 75g or 225 μg/mouse) injected 7 days before exposure of RGCs to glutamate toxicity. The results are presented as mean ± SEM of percentage of RGCs that were protected due to Cop 1 vaccination out of the total RGC death in the non-treated group. * represents statistically significant difference (t-test, $p<0.05$) versus the non-treated group.

Fig. 2 shows the latency of neuroprotective effect on RGCs of mice by vaccination with 75 μg Cop 1 injected 7, 14 and 28 days before exposure of RGCs to glutamate toxicity.

Fig. 3 shows that daily injections of Cop 1 repeated for three days at doses of 25 μg and 75 μg, cause loss of the neuroprotective effect on RGCs (at 25 μg, protection of 23% and 1.5% after 2 and 3 days, respectively; at 75 μg, protection of 47% and 13.5% after 2 and 3 days, respectively).

Fig. 4 shows the efficacy of two repeated injections of Cop 1 (75 μg/mouse), injected at different time intervals (1, 2, 3, 4, 6, 8, weeks). The neuroprotective effect of the treatment on RGCs is represented as % of a single injection of Cop 1 (75 μg/mouse), injected 7 days before induction of glutamate toxicity. This single injection was determined as positive control and performed in each experiment. * represents statistically significant difference (t-test, $p<0.05$) versus the non-treated group.

Fig. 5 shows the efficacy of three repeated injections of Cop 1 (75 μg/mouse) injected at different time intervals (daily, 1, 2, 4, weeks). The neuroprotective effect of the treatment on RGCs is represented as % of a single injection of Cop 1 (75 μg/mouse), injected 7 days before induction of glutamate toxicity. This single injection was determined as positive control and performed in each experiment.

Fig. 6 shows proliferation of splenocytes from mice following immunization with different doses of Cop 1 (25 μg, 75 μg, 225 μg). The results after 7, 14, 21 and

28 days are expressed as stimulation index (SI), where SI is the mean cpm of cells incubated in vitro with Cop 1 divided by the mean cpm of cells incubated in vitro without Cop 1.

Fig. 7 shows INF-γ secretion from stimulated splenocytes 7, 14, 21 or 28 days after immunization with 25 μg or 75 μg Cop 1.

Fig. 8 is a graph showing the rotarod performance of HD R6/2 transgenic mice after vaccination with 75 μg or 150 μg Cop 1.

Fig. 9 shows the rotarod performance of HD R6/2 transgenic mice following vaccination with 150 μg Cop 1, at different speeds of rotation (2, 5, 15 and 25 rpm).

DETAILED DESCRIPTION OF THE INVENTION

The composition of the invention preferably comprises Copolymer 1, most preferably in the form of its acetate salt known under the generic name glatiramer acetate. Glatiramer acetate has been approved in several countries for the treatment of multiple sclerosis (MS) under the trade name, Copaxone® (a trademark of Teva Pharmaceuticals Ltd., Petach Tikva, Israel). In a most preferred embodiment, the composition of the invention is Copaxone®, used for daily administration for treatment of multiple sclerosis, only that for the purpose of the present invention the composition is administered according to a different regimen, as disclosed herein. This composition is administered in a regimen that confers protective autoimmunity and is sometimes referred to herein as a vaccine for neuroprotective vaccination. However, if desired, the vaccine may contain Copolymer 1 emulsified in an adjuvant suitable for human clinical use.

As used herein, the terms "Cop 1" and "Copolymer 1" are used interchangeably. For the purpose of the present invention, "Cop 1 or a Cop 1-related peptide or polypeptide" is intended to include any peptide or polypeptide, including a random copolymer, that cross-reacts functionally with myelin basic protein (MBP) and is able to compete with MBP on the MHC class II in the antigen presentation, and includes the term glatiramer acetate, the active ingredient of Copaxone®.

The composition or vaccine of the invention may comprise as active agent a random copolymer comprising a suitable quantity of a positively charged amino acid such as lysine or arginine, in combination with a negatively charged amino acid (preferably in a lesser quantity) such as glutamic acid or aspartic acid, optionally in combination with a non-charged neutral amino acid such as alanine or glycine, serving as a filler, and optionally with an amino acid adapted to confer on the copolymer immunogenic properties, such as an aromatic amino acid like tyrosine or tryptophan. Such compositions may include any of those copolymers disclosed in WO 00/05250, the entire contents of which being hereby incorporated herein by reference.

More specifically, the composition for use in the present invention comprises at least one copolymer selected from the group consisting of random copolymers comprising one amino acid selected from each of at least three of the following groups: (a) lysine and arginine; (b) glutamic acid and aspartic acid; (c) alanine and glycine; and (d) tyrosine and tryptophan.

The copolymers for use in the present invention can be composed of L- or D-amino acids or mixtures thereof. As is known by those of skill in the art, L-amino acids occur in most natural proteins. However, D-amino acids are commercially available and can be substituted for some or all of the amino acids used to make the terpolymers and other copolymers used in the present invention. The present invention contemplates the use of copolymers containing both D- and L-amino acids, as well as copolymers consisting essentially of either L- or D-amino acids.

In one embodiment of the invention, the copolymer contains four different amino acids, each from a different one of the groups (a) to (d). A preferred copolymer according to this embodiment comprises in combination alanine, glutamic acid, lysine, and tyrosine, of net overall positive electrical charge and of a molecular weight of about 2,000 - 40,000 Da, preferably of about 2,000 -13,000 Da, and is most preferably Copolymer 1 of average molecular weight of about 4,700 - 13,000 Da, but also higher molecular weight forms of Copolymer 1 are encompassed by the present invention. Preferred molecular weight ranges and

processes for making a preferred form of Cop 1 are described in U.S. Patent No. 5,800,808, the entire contents of which being hereby incorporated in the entirety. It is clear that this is given by way of example only, and that the vaccine can be varied both with respect to the constituents and relative proportions of the constituents if the above general criteria are adhered to. Thus, the copolymer may be a polypeptide from about 15 to about 100, preferably from about 40 to about 80, amino acids in length, and is preferably the copolymer having the generic name glatiramer acetate.

In another embodiment, the copolymer contains three different amino acids each from a different one of three groups of the groups (a) to (d). These copolymers are herein referred to as terpolymers.

In one embodiment, the terpolymers for use in the present invention contain tyrosine, alanine, and lysine, hereinafter designated YAK. The average molar fraction of the amino acids in these terpolymers can vary. For example, tyrosine can be present in a mole fraction of about 0.005-0.250; alanine can be present in a mole fraction of about 0.3 - 0.6; and lysine can be present in a mole fraction of about 0.1-0.5. The average molecular weight is between 2,000 - 40,000 Da, and preferably between about 3,000 - 35,000 Da. In a more preferred embodiment, the average molecular weight is about 5,000 - 25,000 Da. It is possible to substitute arginine for lysine, glycine for alanine, and/or tryptophan for tyrosine.

In another embodiment, the terpolymers for use in the present invention contain tyrosine, glutamic acid, and lysine, hereinafter designated YEK. The average molar fraction of the amino acids in these terpolymers can vary: glutamic acid can be present in a mole fraction of about 0.005 - 0.300, tyrosine can be present in a mole fraction of about 0.005-0.250, and lysine can be present in a mole fraction of about 0.3-0.7. The average molecular weight is between 2,000 - 40,000 Da, and preferably between about 3,000 - 35,000 Da. In a more preferred embodiment, the average molecular weight is about 5,000 - 25,000 Da. It is possible to substitute aspartic acid for glutamic acid, arginine for lysine, and/or tryptophan for tyrosine.

In another embodiment the terpolymers for use in the present invention contain lysine, glutamic acid, and alanine, hereinafter designated KEA. The average

molar fraction of the amino acids in these polypeptides can also vary. For example, glutamic acid can be present in a mole fraction of about 0.005 - 0.300, alanine can be present in a mole fraction of about 0.005 - 0.600, lysine can be present in a mole fraction of about 0.2 - 0.7. The average molecular weight is between 2,000 - 40,000 Da, and preferably between about 3,000 - 35,000 Da. In a more preferred embodiment, the average molecular weight is about 5,000 - 25,000 Da. It is possible to substitute aspartic acid for glutamic acid, glycine for alanine, and/or arginine for lysine.

In another embodiment, the terpolymers for use in the present invention contain tyrosine, glutamic acid, and alanine, hereinafter designated YEA. The average molar fraction of the amino acids in these polypeptides can vary. For example, tyrosine can be present in a mole fraction of about 0.005 - 0.250, glutamic acid can be present in a mole fraction of about 0.005 - 0.300, and alanine can be present in a mole fraction of about 0.005 - 0.800. The average molecular weight is between 2,000 - 40,000 Da, and preferably between about 3,000 - 35,000 Da. In a more preferred embodiment, the average molecular weight is about 5,000 - 25,000 Da. It is possible to substitute tryptophan for tyrosine, aspartic acid for glutamic acid, and/or glycine for alanine.

In a more preferred embodiment, the mole fraction of amino acids of the terpolymers is about what is preferred for Copolymer 1. The mole fraction of amino acids in Copolymer 1 is glutamic acid about 0.14, alanine about 0.43, tyrosine about 0.10, and lysine about 0.34. The most preferred average molecular weight for Copolymer 1 is between about 5,000 - 9,000 Da. The activity of Copolymer 1 for the vaccine disclosed herein is expected to remain if one or more of the following substitutions is made: aspartic acid for glutamic acid, glycine for alanine, arginine for lysine, and tryptophan for tyrosine.

The molar ratios of the monomers of the more preferred terpolymer of glutamic acid, alanine, and tyrosine, or YEA, is about 0.21 to about 0.65 to about 0.14.

The molar ratios of the monomers of the more preferred terpolymer of glutamic acid, alanine and lysine, or KEA, is about 0.15 to about 0.48 to about 0.36.

The molar ratios of the monomers of the more preferred terpolymer of glutamic acid, tyrosine, and lysine, or YEK, is about 0.26 to about 0.16 to about 0.58.

The molar ratios of the monomers of the more preferred terpolymer of tyrosine, alanine and lysine, or YAK, is about 0.10 to about 0.54 to about 0.35.

The terpolymers can be made by any procedure available to one of skill in the art. For example, the terpolymers can be made under condensation conditions using the desired molar ratio of amino acids in solution, or by solid phase synthetic procedures. Condensation conditions include the proper temperature, pH, and solvent conditions for condensing the carboxyl group of one amino acid with the amino group of another amino acid to form a peptide bond. Condensing agents, for example dicyclohexylcarbodiimide, can be used to facilitate the formation of the peptide bond. Blocking groups can be used to protect functional groups, such as the side chain moieties and some of the amino or carboxyl groups against undesired side reactions.

For example, the process disclosed in U.S. Patent 3,849,650, can be used wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and N ε-trifluoroacetyl-lysine are polymerized at ambient temperatures in anhydrous dioxane with diethylamine as an initiator. The γ-carboxyl group of the glutamic acid can be deblocked by hydrogen bromide in glacial acetic acid. The trifluoroacetyl groups are removed from lysine by 1 molar piperidine. One of skill in the art readily understands that the process can be adjusted to make peptides and polypeptides containing the desired amino acids, that is, three of the four amino acids in Copolymer 1, by selectively eliminating the reactions that relate to any one of glutamic acid, alanine, tyrosine, or lysine. For purposes of this application, the terms "ambient temperature" and "room temperature" mean a temperature ranging from about 20 to about 26°C.

The molecular weight of the terpolymers can be adjusted during polypeptide synthesis or after the terpolymers have been made. To adjust the molecular weight during polypeptide synthesis, the synthetic conditions or the amounts of amino acids are adjusted so that synthesis stops when the polypeptide reaches the approximate length which is desired. After synthesis, polypeptides with the desired molecular weight can be obtained by any available size selection procedure, such as chromatography of the polypeptides on a molecular weight sizing column or gel, and collection of the molecular weight ranges desired. The present polypeptides can also be partially hydrolyzed to remove high molecular weight species, for example, by acid or enzymatic hydrolysis, and then purified to remove the acid or enzymes.

In one embodiment, the terpolymers with a desired molecular weight may be prepared by a process, which includes reacting a protected polypeptide with hydrobromic acid to form a trifluoroacetyl-polypeptide having the desired molecular weight profile. The reaction is performed for a time and at a temperature which is predetermined by one or more test reactions. During the test reaction, the time and temperature are varied and the molecular weight range of a given batch of test polypeptides is determined. The test conditions which provide the optimal molecular weight range for that batch of polypeptides are used for the batch. Thus, a trifluoroacetyl-polypeptide having the desired molecular weight profile can be produced by a process, which includes reacting the protected polypeptide with hydrobromic acid for a time and at a temperature predetermined by test reaction. The trifluoroacetyl-polypeptide with the desired molecular weight profile is then further treated with an aqueous piperidine solution to form a low toxicity polypeptide having the desired molecular weight.

In a preferred embodiment, a test sample of protected polypeptide from a given batch is reacted with hydrobromic acid for about 10-50 hours at a temperature of about 20-28°C. The best conditions for that batch are determined by running several test reactions. For example, in one embodiment, the protected polypeptide is reacted with hydrobromic acid for about 17 hours at a temperature of about 26°C.

As binding motifs of Cop 1 to MS-associated HLA-DR molecules are known (Fridkis-Hareli et al, 1999), polypeptides of fixed sequence can readily be prepared and tested for binding to the peptide binding groove of the HLA-DR molecules as described in the Fridkis-Hareli et al (1999) publication. Examples of such peptides are those disclosed in WO 00/05249 and WO 00/05250, the entire contents of which being hereby incorporated herein by reference. Thirty-two of the peptides specifically disclosed in said application are reproduced in **Table 1**, hereinbelow. Such peptides and other similar peptides would be expected to have similar activity as Cop 1. Such peptides, and other similar peptides, are also considered to be within the definition of Cop 1-related peptides or polypeptides and their use is considered to be part of the present invention.

The definition of "Cop 1 related-polypeptide" according to the invention is meant to encompass other synthetic amino acid copolymers such as the random four-amino acid copolymers described by Fridkis-Hareli et al., 2002, as candidates for treatment of multiple sclerosis, namely copolymers (14-, 35- and 50-mers) containing the amino acids phenylalanine, glutamic acid, alanine and lysine (poly FEAK), or tyrosine, phenylalanine, alanine and lysine (poly YFAK), and any other similar copolymer to be discovered that can be considered a universal antigen similar to Cop 1.

Table 1

SEQ ID NO.	Peptide Sequence
1	AAAYAAAAAAKAAAA
2	AEKYAAAAAAKAAAA
3	AKEYAAAAAAKAAAA
4	AKKYAAAAAAKAAAA
5	AEAYAAAAAAKAAAA
6	KEAYAAAAAAKAAAA
7	AEEYAAAAAAKAAAA
8	AAEYAAAAAAKAAAA
9	EKAYAAAAAAKAAAA
10	AAKYEAAAAAKAAAA
11	AAKYAEAAAAKAAAA
12	EAAYAAAAAAKAAAA
13	EKKYAAAAAAKAAAA

14	EAKYAAAAAAKAAAA
15	AEKYAAAAAAAAAAA
16	AKEYAAAAAAAAAAA
17	AKKYEAAAAAAAAAA
18	AKKYAEAAAAAAAAA
19	AEAYKAAAAAAAAAA
20	KEAYAAAAAAAAAAA
21	AEEYKAAAAAAAAAA
22	AAEYKAAAAAAAAAA
23	EKAYAAAAAAAAAAA
24	AAKYEAAAAAAAAAA
25	AAKYAEAAAAAAAAA
26	EKKYAAAAAAAAAAA
27	EAKYAAAAAAAAAAA
28	AEYAKAAAAAAAAAA
29	AEKAYAAAAAAAAAA
30	EKYAAAAAAAAAAAA
31	AYKAEAAAAAAAAAA
32	AKYAEAAAAAAAAAA

Various mouse models for Huntington's disease have been established which enable the exploration of early pathological, molecular and cellular abnormalities produced by the CAG mutation.

The HD R6/2 transgenic mice model was selected as the *in vivo* test system in the present invention. These mice overexpress exon 1 of the human Huntington's disease gene with an increased CAG repeat length that encodes huntingtin (Mangiarini et al., 1996). HD R6/2 transgenic mice show behavioral-motor deficits at as early as 5-6 weeks of age. Behavioral anomalies do not appear until 8 weeks, followed by the development of a progressive severe neurological phenotype with low weight, clasping, tremor and convulsions, and an early death at 10-14 weeks (Carter et al., 1999).

Based on the glutamate toxicity model, an optimal neuroprotective effect in mice was established by a regimen of repeated injections of 75 μg Cop 1 at 4 weeks interval. The same regimen of treatment was found beneficial to HD R6/2 transgenic mice and reduced the rate of motor function deterioration, as shown by a

significant preservation of the rotarod performance and prolonged life span of the animals.

The dosage of Cop 1 to be administered will be determined by the physician according to the age of the patient and stage of the disease and may be chosen from a range of 10-80 mg, preferably 20 mg, although any other suitable dosage is encompassed by the invention. The treatment should be preferably carried out by administration of repeated doses at suitable time intervals, preferably every 4 or 6 weeks, but any other suitable interval between the immunizations is envisaged by the invention according to the condition of the patient.

The composition of the invention may be administered by any suitable mode of administration, including orally, intramuscularly, subcutaneously and intradermally, with or without adjuvant.

The following examples illustrate certain features of the present invention but are not intended to limit the scope of the present invention.

EXAMPLES

Materials and Methods

Animals. Mice of the C57BL/6J strain, aged 8-13 weeks, were supplied by the Animal Breeding Center of The Weizmann Institute of Science (Rehovot, Israel). Prior to their use in the experiments, the mice were anesthetized by intraperitoneal administration of 80 mg/kg ketamine and 16 mg/kg xylazine. Transgenic R6/2 mice overexpressing the human gene encoding huntingtin were obtained from the Jackson Laboratory. All animals were handled according to the regulations formulated by the Institutional Animal Care and Use Committee (IACUC).

Materials. Cop 1 (median MW: 7,200 dalton) was from Teva Pharmaceutical Industries Ltd. (Petach Tikva, Israel).

Immunization. For immunization, Cop 1 dissolved in PBS (100 μl) was injected subcutaneously (SC) at one site in the flank of the mice. Control mice were injected with vehicle only.

Glutamate injection. The right eye of an anesthetized C57B BL/6J mouse was punctured with a 27-gauge needle in the upper part of the sclera, and a 10-µl Hamilton syringe with a 30-gauge needle was inserted as far as the vitreal body. Mice were injected intraocularly with a total volume of 1 µl (200 nmol) of L-glutamate dissolved in saline.

Labeling of retinal ganglion cells (RGC) in mice. RGCs were labeled 72 hours before the end of the experiment. Mice were anesthetized and placed in a stereotactic device. The skull was exposed and kept dry and clean. The bregma was identified and marked. The designated point of injection was at a depth of 2 mm from the brain surface, 2.92 mm behind the bregma in the anteroposterior axis and 0.5 mm lateral to the midline. A window was drilled in the scalp above the designated coordinates in the right and left hemispheres. The neurotracer dye FluoroGold (5% solution in saline; Fluorochrome, Denver, CO) was then applied (1 µl, at a rate of 0.5 µl/min in each hemisphere) using a Hamilton syringe, and the skin over the wound was sutured. Retrograde uptake of the dye provides a marker of the living cells.

Assessment of RGC survival in mice. Mice were given a lethal dose of pentobarbitone (170 mg/kg). Their eyes were enucleated and the retinas were detached and prepared as flattened whole mounts in paraformaldehyde (4% in PBS). Labeled cells from 4–6 selected fields of identical size (0.5 mm^2) were counted. The selected fields were located at approximately the same distance from the optic disk (0.3 mm) to overcome the variation in RGC density as a function of distance from the optic disk. Fields were counted under the fluorescence microscope (magnification ×900) by observers blinded-to-the-treatment received by the mouse. The average number of RGCs per field in each retina was calculated. The effectiveness of the different vaccine formulations in protecting neurons is measured by counting the surviving RGCs.

Example 1. Glutamate toxicity - an in vivo model for selection of dose and regimen of Cop 1 vaccination

Glutamate is an amino acid normally present at low concentrations in the CNS, where it serves as the principal excitatory neurotransmitter. However, in many neurodegenerative diseases, glutamate levels rise to toxic levels, causing cell damage. This model was therefore chosen to establish Cop 1 neuroprotective vaccination and optimize the therapeutic regimen. Glutamate toxicity is assessed by intraocular injection of glutamate into the eyes of C57Bl/6J mice and then measuring the subsequent death of Retinal Ganglion Cells (RGCs), the neurons that carry visual signals to the brain.

1a. Cop 1 dose determination

To study the effect of the dose of Cop 1 vaccination on glutamate-induced RGC death, Cop 1 emulsified in CFA (25, 75 or 225 μg Cop 1 in total volume of 100 μl) was injected subcutaneously at one site in the flank of C57BL/6J mice, and seven days later glutamate (200 nmol) was injected into the vitreal body of the mice. After seven days the surviving RGCs were counted. The amount of RGCs death following glutamate toxicity without any prior immunization was taken as 100% of protectable cells. The results, presented in **Fig. 1,** show that effective vaccination was obtained by treatment with either 25 μg or 75 μg Cop 1.

Latency of neuroprotective effect was determined by vaccination with 75 μg Cop 1 seven, fourteen and twenty-eight days prior to glutamate injection. As can be seen in **Fig. 2,** the neuroprotective effect of a single injection of Cop 1 is optimal at 7 days post-immunization (reduction of RGC death by ≥ 40%). The neuroprotective effect was reduced 14 and 28 days after vaccination.

1b. Optimal regimen of repeated Cop 1 injections

In an attempt to maintain the neuroprotective effect of Cop 1 immunization, repeated injections of Cop 1 were evaluated. The aim was to determine the optimal regimen of repeated Cop 1 injections that will maximize the long term RGCs survival effect.

Cop 1 was originally developed as a therapy for multiple sclerosis (MS), an autoimmune disease characterized by unregulated T-cell activity against self-peptides of the CNS. Cop 1 is given to MS patients once a day at a dosage of 20 mg per patient by subcutaneous injections. We examined if daily injections of Cop 1 repeated for several days can maintain the neuroprotective effect on RGCs. Mice were immunized with Cop 1 daily for two or three days (Cop 1, 25 μg/mouse and 75 μg/mouse). The results, presented in **Fig. 3,** show that daily injections of Cop 1 repeated for two days, give neuroprotection on RGCs and better protection is achieved with 75 μg Cop 1, while immunization during three consecutive days cause loss of the neuroprotective effect on RGCs.

To determine the vaccination regimen (best time interval) that produces the optimal degree of neuroprotection, three repeated Cop 1 injections were administered to mice at different time intervals ranging from daily to monthly. In one experiment, the mice received two 75 μg Cop 1 injections at intervals of 1, 2, 3, 4, 6 and 8 weeks. In another experiment, the mice received three repeated 75 μg Cop 1 injections daily or at intervals of 1, 2, and 4 weeks. The results are shown in **Figs. 4** and **5,** respectively. The neuroprotective effect of the treatment is represented as % of a single injection of Cop 1 (75 μg/mouse) injected 7 days before glutamate toxicity was induced. This single injection was determined as positive control and was performed in each experiment. As shown in Figs. 4 and 5, a 4-week interval between Cop 1 injections (75 μg/mouse) had the highest neuroprotective efficacy. It is striking that daily administration of Cop 1, the regimen used as therapy for multiple sclerosis, provides poor neuroprotection.

The results using the glutamate toxicity model showed that the regimen of repeated injections of Cop 1 may lead to a sustained neuroprotective effect. Based on these results, the optimal neuroprotective effect in mice was found to be repeated 75μg injections of Cop 1 at 4 week intervals.

Example 2. Correlation between the cellular immune response to Cop 1 vaccination and the neuroprotective effect

Two *ex vivo* markers correlate with the efficacy – the T cell stimulation index, and interferon-γ (IFN-γ). The stimulation index indicates the extent to which Cop-1-responsive T cells are present in the lymphocyte population. IFN-γ secretion is characteristic of T cells of the "Th1" subtype. These markers thus provide a means of profiling the cellular immune response.

The correlation between the neuroprotective effect and the cellular immune response to Cop 1 vaccination was thus determined by *in vitro* evaluation of T-cell proliferation and the level –profile of cytokine secretion.

The effect of Cop 1 vaccination was examined by isolating splenic lymphocytes from mice immunized with different doses of Cop 1 (25, 75 and 225 μg/mouse), 7, 14, 21 and 28 days after immunization, and measuring the proliferative response of the splenocytes to Cop 1 by [^{3}H]thymidine incorporation, and the induction of cytokine production (IFN-γ) by ELISA assay.

Uptake of labeled thymidine by splenocytes represents proliferation of specific T-cells to Cop 1, following Cop 1 vaccination. The results in **Fig. 6** are expressed as stimulation index (SI), where SI is the mean cpm of cells incubated in vitro with the antigen (Cop 1) divided by the mean cpm of cells incubated in vitro without the antigen (Cop 1). A positive response was defined as SI>2. A single injection of Cop 1 resulted in increased SI after 7 days for the three doses. After 14 days, only marginal proliferation of T-cells was seen for injection of 25 and 225 μg Cop 1 and less proliferation for injection of 75 μg Cop 1. The SI decreased after 21 and 28 days, meaning that the splenocytes proliferation in response to Cop 1 had abated. These results corroborate the glutamate toxicity results that showed that the neuroprotective efficacy decreases with time.

Secretion of INF-γ cytokine by stimulated splenocytes was measured by ELISA (R&D Systems). As shown in **Fig. 7**, the highest level of INF-γ secretion from splenocytes was observed 7 days after Cop 1 immunization (25 and 75 μg /mouse). The levels of INF-γ declined after 14, 21 and 28 days. These results are in agreement with the results obtained for neuroprotective efficacy and T-cell proliferation.

Neuroprotective efficacy was correlated with IFNγ secretion, similar to the effect shown in Figure 1. In contrast, T-cell proliferation remains high under daily injections of Cop-1. This result shows that while Cop-1 responsive T cells are still present, the loss of IFNγ secretion indicates a shift in the predominant phenotype of the cells; this is accompanied by a loss of neuroprotective efficacy. It therefore appears that neuroprotection is associated with IFNγ secretion.

The above animal results are in line with the observation that daily injections of Copaxone® to MS patients leads to a Th2 type response (Vieira et al., 2003). Thus, the daily regimen of Cop-1 should not be expected to confer neuroprotection and is not the regimen of choice for Huntington's disease; vaccinations spaced at wider intervals are more likely to prove effective.

Example 3. In vivo animal test system for Huntington's disease

The beneficial effect of Cop 1 vaccination was examined for exertion of neuroprotective effects using the HD R6/2 transgenic mice test system. R6/2 transgenic mice over express the mutated human huntingtin gene that includes the insertion of multiple CAG repeats (Mangiarini et al., 1996). These mice show progressive behavioral-motor deficits starting as early as 5-6 weeks of age, and leading to premature death at 10-13 weeks. The symptoms include low body weight, clasping, tremor and convulsions (Carter et al., 1999).

Two different doses of Cop 1 vaccination were tested, 75 μg Cop 1/mouse (n=13) and 150 μg Cop 1/mouse (n=11), that were injected when the mice were 45 days old and every 4 weeks thereafter. A third group (n=12) was vaccinated with 75 μg Cop 1 /mouse on day 60 of age and every 4 weeks thereafter. The control group (n=17) was injected with PBS starting on day 45 of age and every 4 weeks thereafter. Motor neurological functions were evaluated using the rotarod performance test which assesses the capacity of the mice to stay on a rotating rod. For this test, mice were placed on a rod rotating at 2 rpm: the time until the mouse falls off the rotating rod (best of three attempts, up to 180 sec for each trial), is used

as the measure of animal motor-function. Each mouse was tested twice weekly and the two scores averaged.

The results are shown in **Fig. 8**. Each point on the graphs represents the average group score for each week (SEM indicated by error bar). The arrows on the x-axis represent the timing of Cop 1 (or PBS) injections. The results show that vaccination with Cop 1, either 75 µg/mouse or 150 µg/mouse, starting on day 45 of age, produced a significant improvement in motor performance during the follow-up period of 8 to 14 weeks. However, vaccination with 75 µg Cop 1/mouse starting on day 60 of age had no significant effect (data not shown).

Control and Cop 1 vaccinated HD R6/2 transgenic mice (150 µg/mouse) were subjected to rotarod performance test on day 45 using four different speeds: 2. 5, 15 and 25 rpm. **Fig. 9** shows that the improvement in rotarod performance following Cop 1 vaccination is dependent on the speed of rotation. Significant better performance of the twelve-week old vaccinated HD R6/2 mice compared to non-treated HD R6/2 control mice was most clearly apparent using 5 rpm rotarod speed.

The effect of Cop 1 vaccination on weight loss of HD R6/2 transgenic mice was tested on the three groups. Mice were weighed twice a week at the same time during the day. No effect on body weight was observed following vaccination on day 45 or day 60 using either 75 µg/mouse or 150 µg/mouse Cop 1 compared to the control group.

It could also be observed that Cop 1 vaccination significantly delayed mortality and onset of disease of HD R6/2 mice. The effect of Cop 1 vaccination on survival of the HD transgenic mice is shown in **Table 2**. Statistical comparisons of survival were made by ANOVA followed by the Fisher's least significant difference test.

Table 2: Effects of Cop 1 vaccination on survival of HD R6/2 mice

	Control	Cop 1 75 µg/mouse day 45	Cop 1 150 µg/mouse day 45	Cop 1 75 µg/mouse day 60
Survival (days)	103±2.5	110±2.7*	101±3.5	108±1.6
Onset of disease	78±3.8	89±4.5 (p=0.065)	91±3.7*	79±5.6

In conclusion, the results of Examples 1 and 2 show that Cop 1 vaccination attenuates neuronal cell death induced by exposure to elevated levels of the excitotoxic neurotransmitter glutamate, and that the neuroprotective effect is dependent upon activation and proliferation of T-cells specific to Cop 1 that secrete INF-γ (Th1). The neuroprotective effect is short-lived, unless maintained by a boosting regime – it is build up by 7 days post immunization, and is then reduced due to activation of regulatory cells which terminate the response. The Cop 1 dose found to be the most active in the animal models was 75 µg Cop 1/mouse, that translate to a human adult dose of 20 mg on a mg/m^2 basis. The optimal regimen for neuroprotection in mice was monthly injection, both in the glutamate toxicity model and to reduce the rate of motor function deficits and to improve life expectancy in the HD R6/2 transgenic mice (Example 3). Thus, for human use, neuroprotective Cop 1 vaccination should be administered in doses spaced at least one month apart, preferably 5-6 weeks apart, more preferably every 6 weeks.

Example 4. Human clinical trials for Huntington's disease

The primary objective of the human study is to evaluate the tolerability, safety and immunological response of the serial administration of 20 mg or 2x20 mg dose of Cop 1 (Copaxone®) versus placebo, in patients suffering from Huntington's disease. The secondary objective of the study is to evaluate the neurological course of patients with HD disease following administration of Cop 1, by measuring the following neurological clinical parameters: Unified Huntington's Disease Rating Scale (UHDRS) and Total Motor Scale (TMS).

Eligible patients (female and male, 18-70 years old, symptomatic patients with clinically diagnosed HD and a confirmatory family history of HD) will receive one administration of placebo (40 mg mannitol/injection) and three administrations of Copaxone® (20 mg/ml subcutaneously or 2x20 mg/ml subcutaneously, 1 in each arm) at 6 weeks intervals between administrations. Blood samples for immunological profile analysis will be taken at screening and prior to first injection. Each administration of Copaxone® will be followed by a series of blood sampling to determine the immunological profile on days 7, 14, 28 and just prior to next injection and termination.

UHDRS is a research tool that has been developed by the Huntington Study Group (HSG). The purpose of the scale is to allow the researchers to grade the symptoms of HD in a way that allows them to make accurate comparisons between individual patients, and to better chart the course of the disease in patients. The scale is divided into a number of different subscales, including the Total Motor Score 4 (TMS-4). In the human trial, a primary end-point is the change over a period of time, e.g. one-year period, in the TMS-4 subscale of the UHDRS, the standard rating scale for trials in HD. The pre-determined and end-points of the trial (such as UHDRS scores) are compared for the patients on Copaxone and the one may assume the possibility that the drug can be said to have had some kind of impact on Huntington's disease.

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CLAIMS:

1. A method for treatment of a patient suffering from Huntington's disease, which comprises immunizing said patient with an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide.

2. A method for treatment of Huntington's disease which comprises administering to a patient in need a therapeutically effective amount of an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide.

3. A method according to claim 1 or 2, wherein said agent is Copolymer 1.

4. A method for reducing disease progression, and/or for protection from neurodegeneration and/or protection from glutamate toxicity in a patient suffering from Huntington's disease, which comprises immunizing said patient with an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide.

5. A method for reducing disease progression, and/or for protection from neurodegeneration and/or protection from glutamate toxicity in a patient suffering from Huntington's disease, which comprises administering to said patient in need a therapeutically effective amount of an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide.

6. A method according to claim 4-5, wherein said active agent is Copolymer 1.

7. A method according to any one of claims 1 to 6, wherein said agent is administered once every 4-6 weeks.

8. A method according to claim 7, wherein said agent is Copolymer 1 that is administered once every 6 weeks.

9. A pharmaceutical composition for treatment of Huntington's disease comprising a pharmaceutically acceptable carrier and an active agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide.

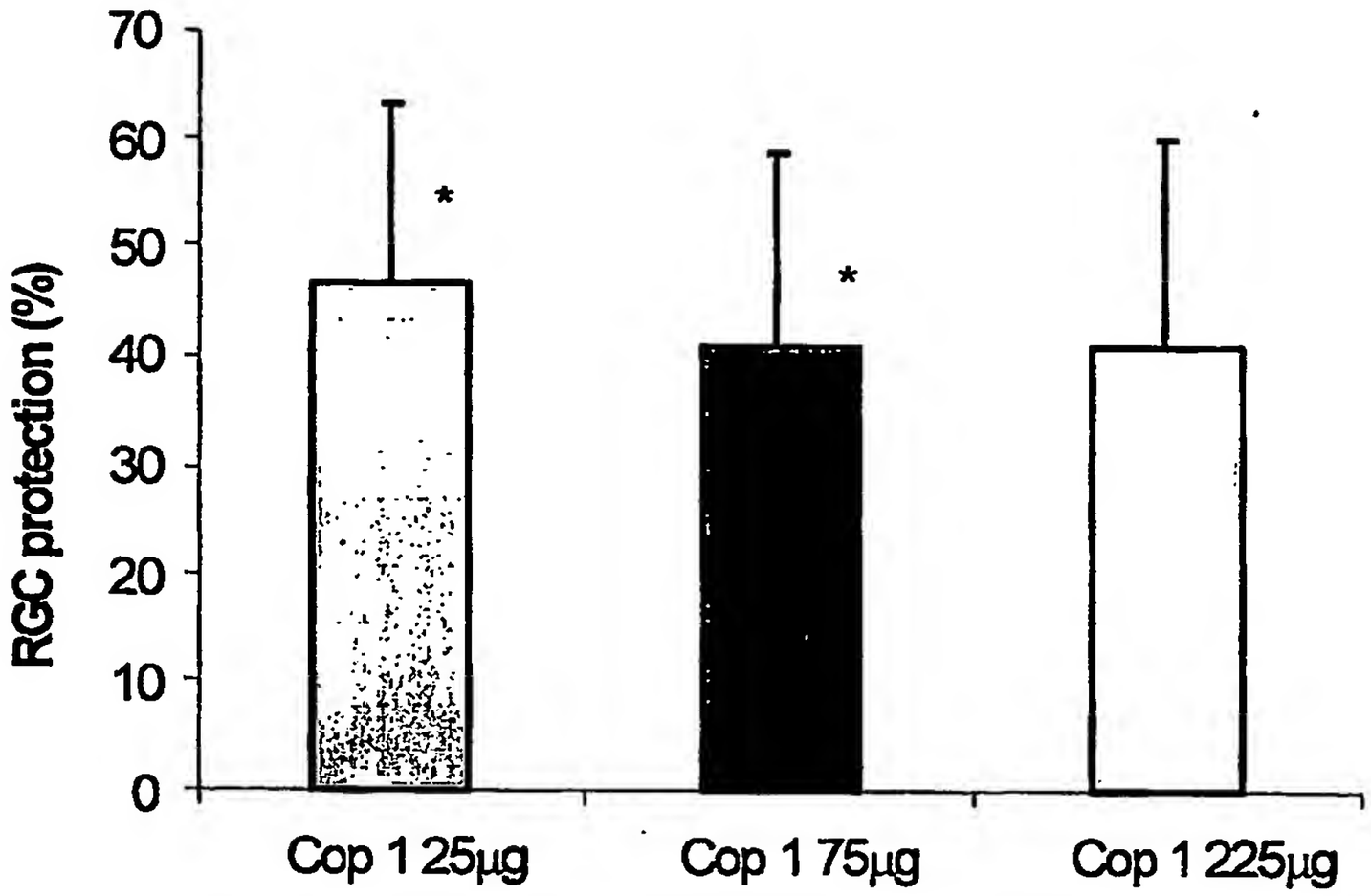
10. A pharmaceutical composition according to claim 9, for reducing disease progression, and/or for protection from neurodegeneration, and/or protection from glutamate toxicity in Huntingon's disease patients.

11. A pharmaceutical composition according to claim 9 or 10, wherein said active agent is Copolymer 1.

12. Use of an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide, for the preparation of a pharmaceutical composition for treatment of Huntington's disease

13. Use of an agent selected from the group consisting of Copolymer 1, a Copolymer 1-related peptide, and a Copolymer 1-related polypeptide, for the preparation of a pharmaceutical composition for reducing disease progression, and/or for protection from neurodegeneration, and/or protection from glutamate toxicity in Huntington's disease patients.

14. Use according to claim 12 or 13 wherein said active agent is Copolymer 1.


RGC protection (%)
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60
50
40
30
20
10
0
*
*
Cop 1 25µg
Cop 1 75µg
Cop 1 225µg

Fig. 1

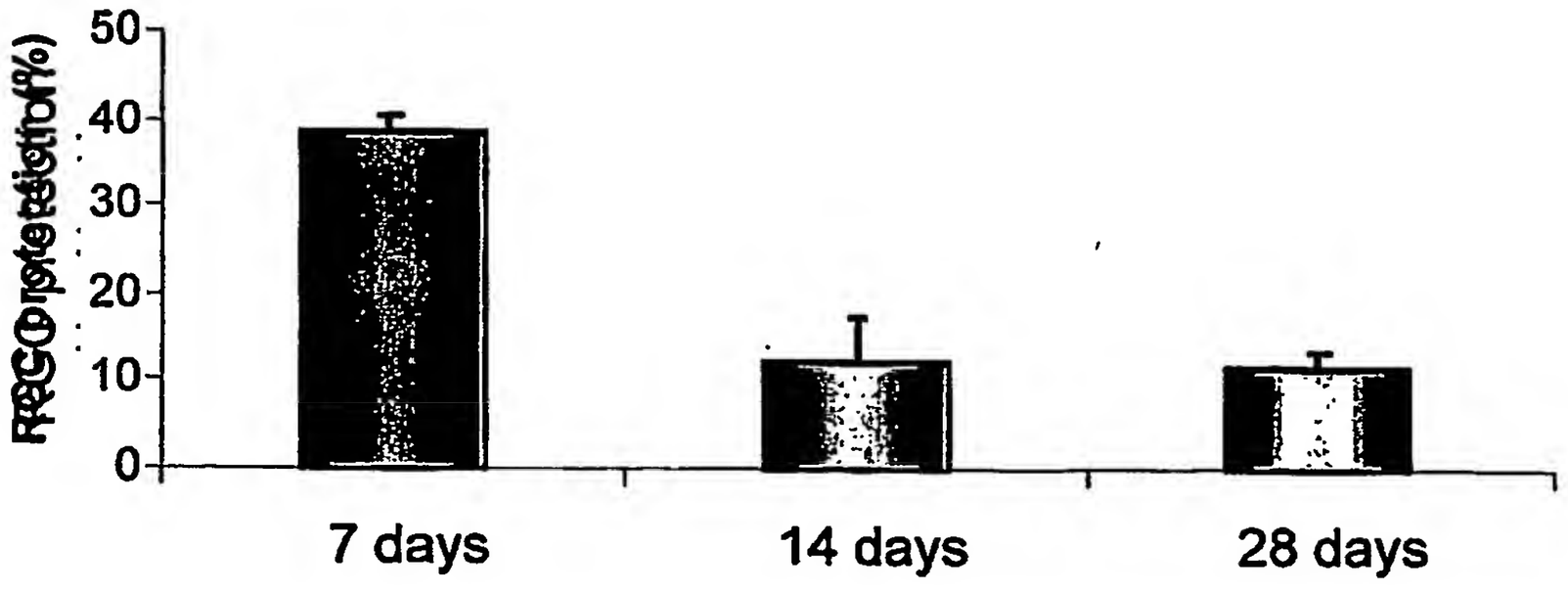
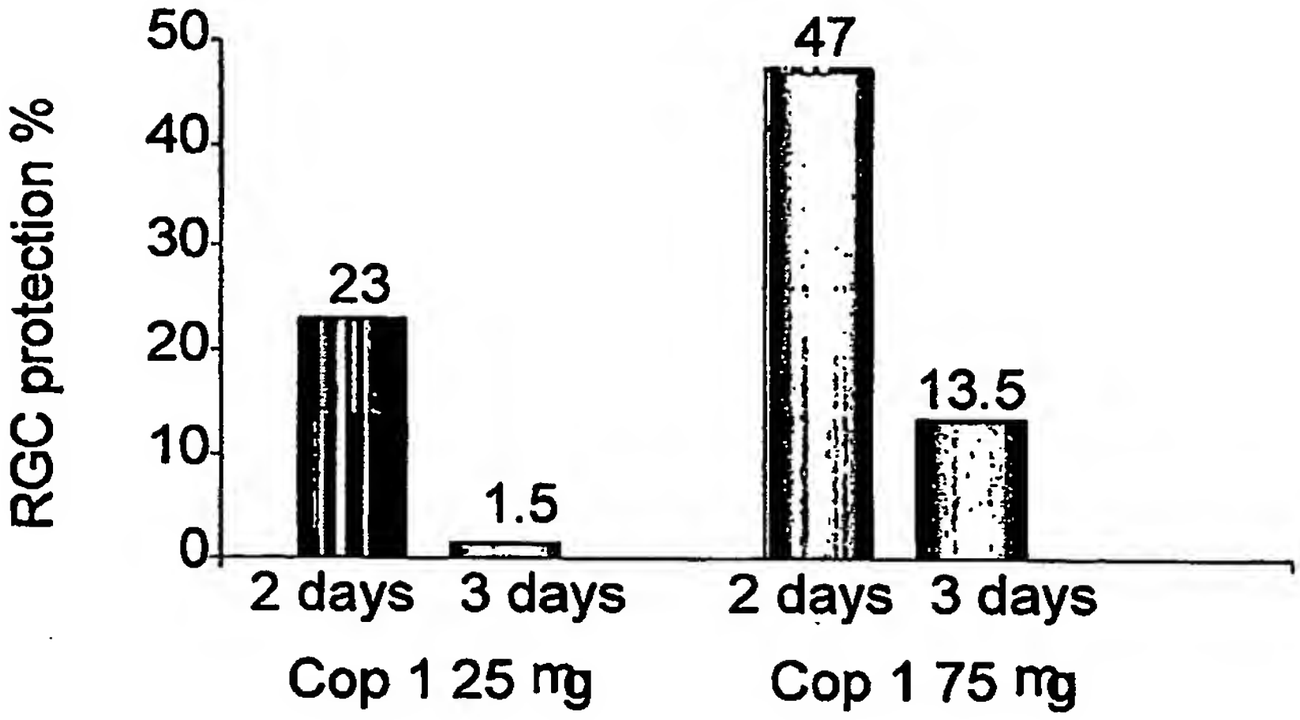

50
40
30
20
10
0
7 days
14 days
28 days

Fig. 2


RGC protection %
50
40
30
20
10
0
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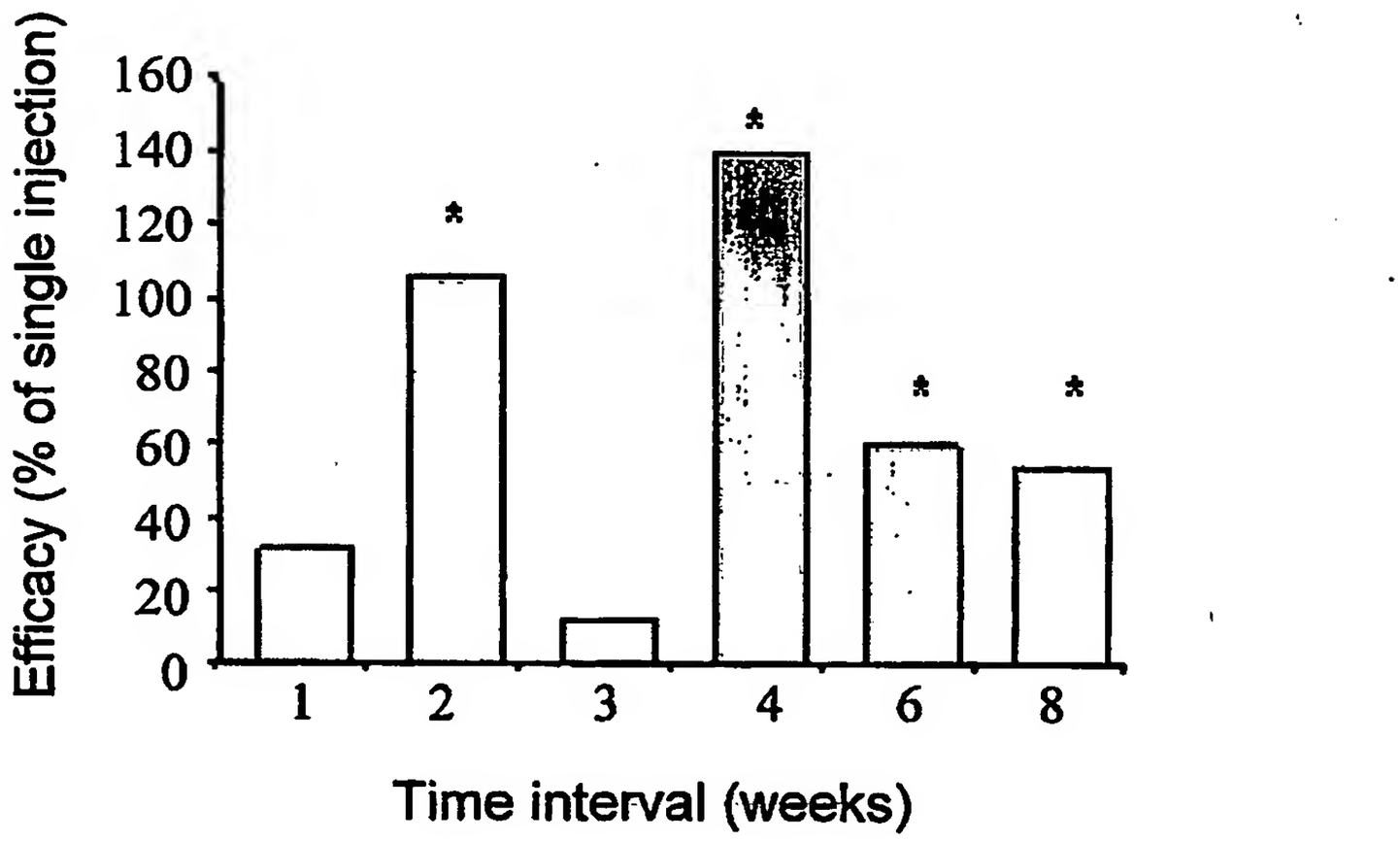
47
13.5
2 days
3 days
2 days
3 days
Cop 1 25 mg
Cop 1 75 mg

Fig. 3


Efficacy (% of single injection)
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120
100
80
60
40
20
0
1
2
3
4
6
8
Time interval (weeks)

Fig. 4

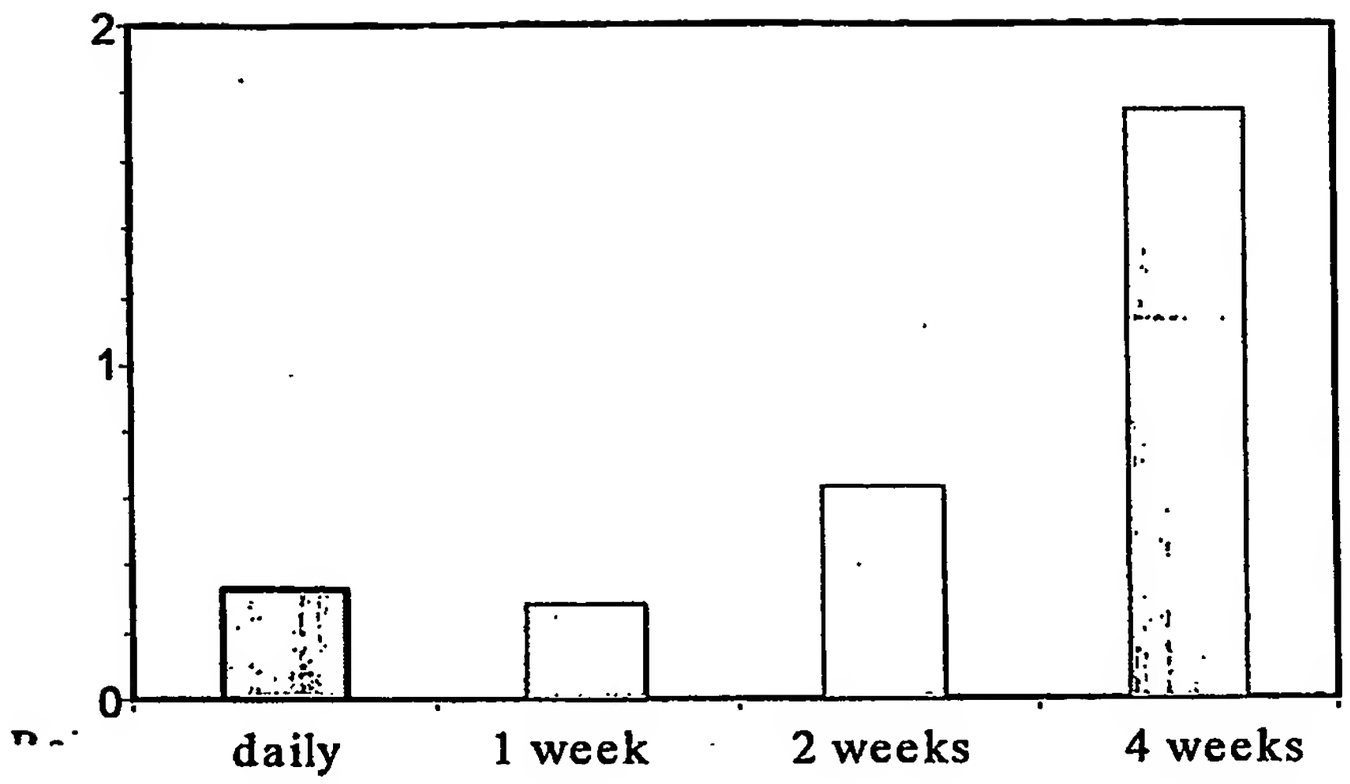
2
1
0
daily
1 week
2 weeks
4 weeks

Fig. 5

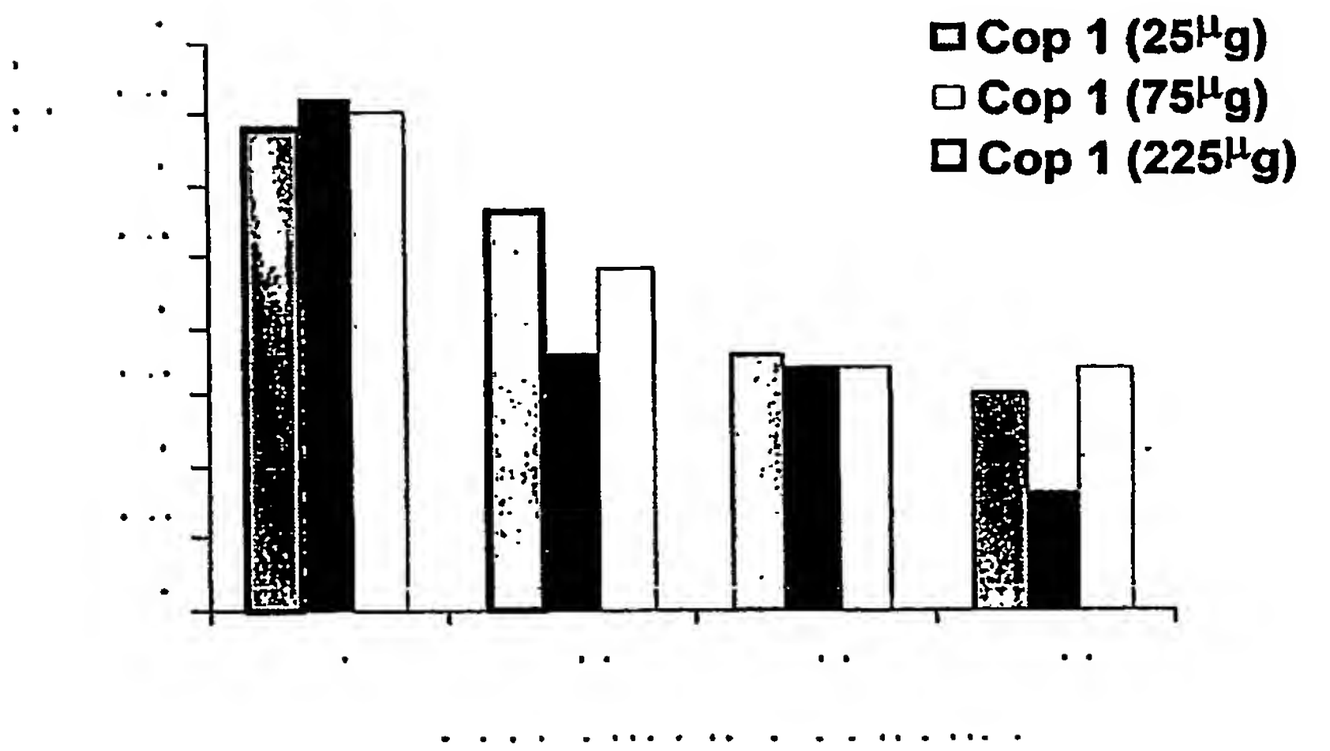
Cop 1 (25μg)
Cop 1 (75μg)
Cop 1 (225μg)

Fig. 6

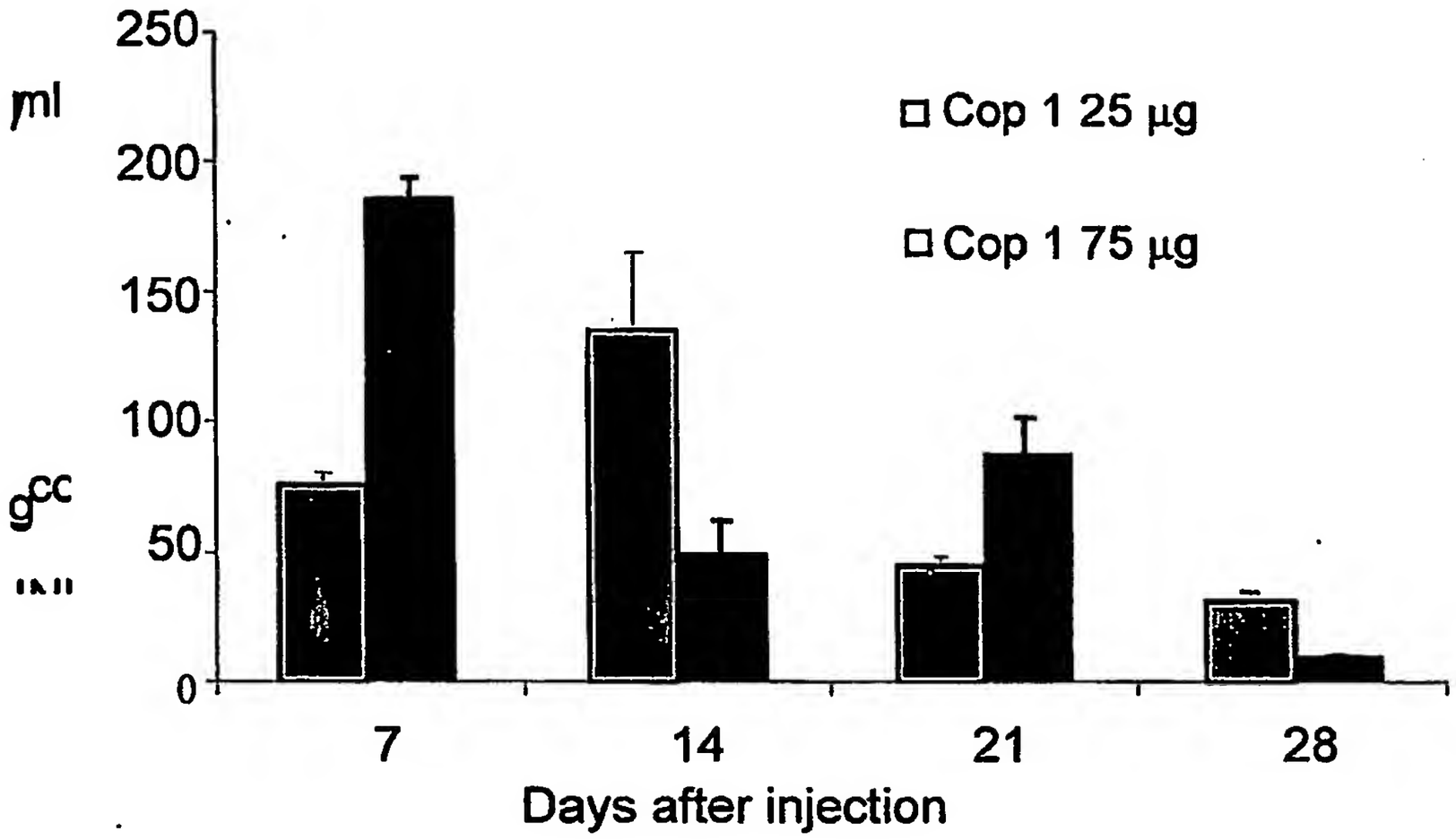
250
200
150
100
50
0
ml
Cop 1 25 µg
Cop 1 75 µg
7
14
21
28
Days after injection

Fig. 7

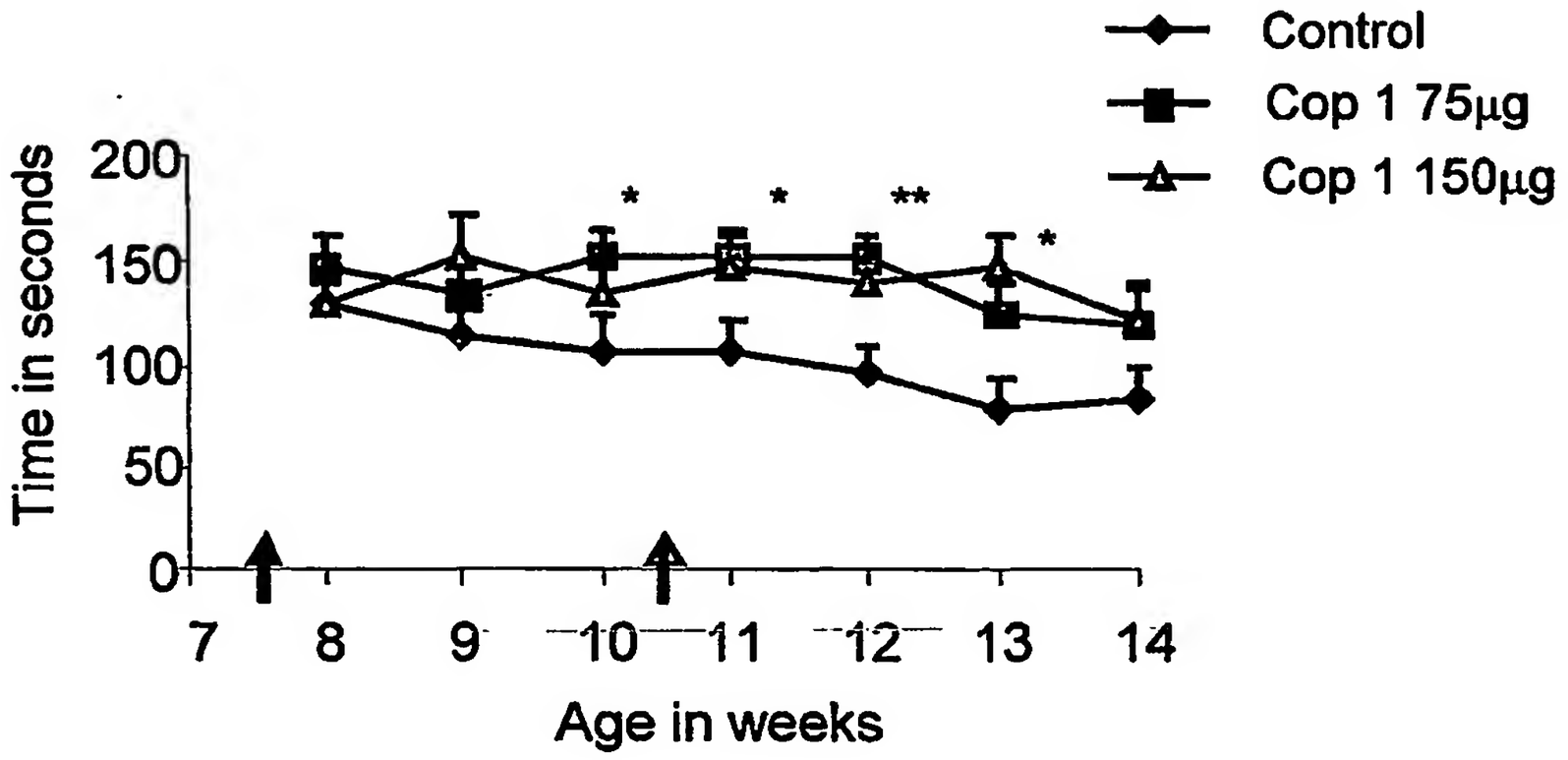
Control
Cop 1 75µg
Cop 1 150µg
200
150
100
50
0
Time in seconds
7
8
9
10
11
12
13
14
Age in weeks

Fig. 8

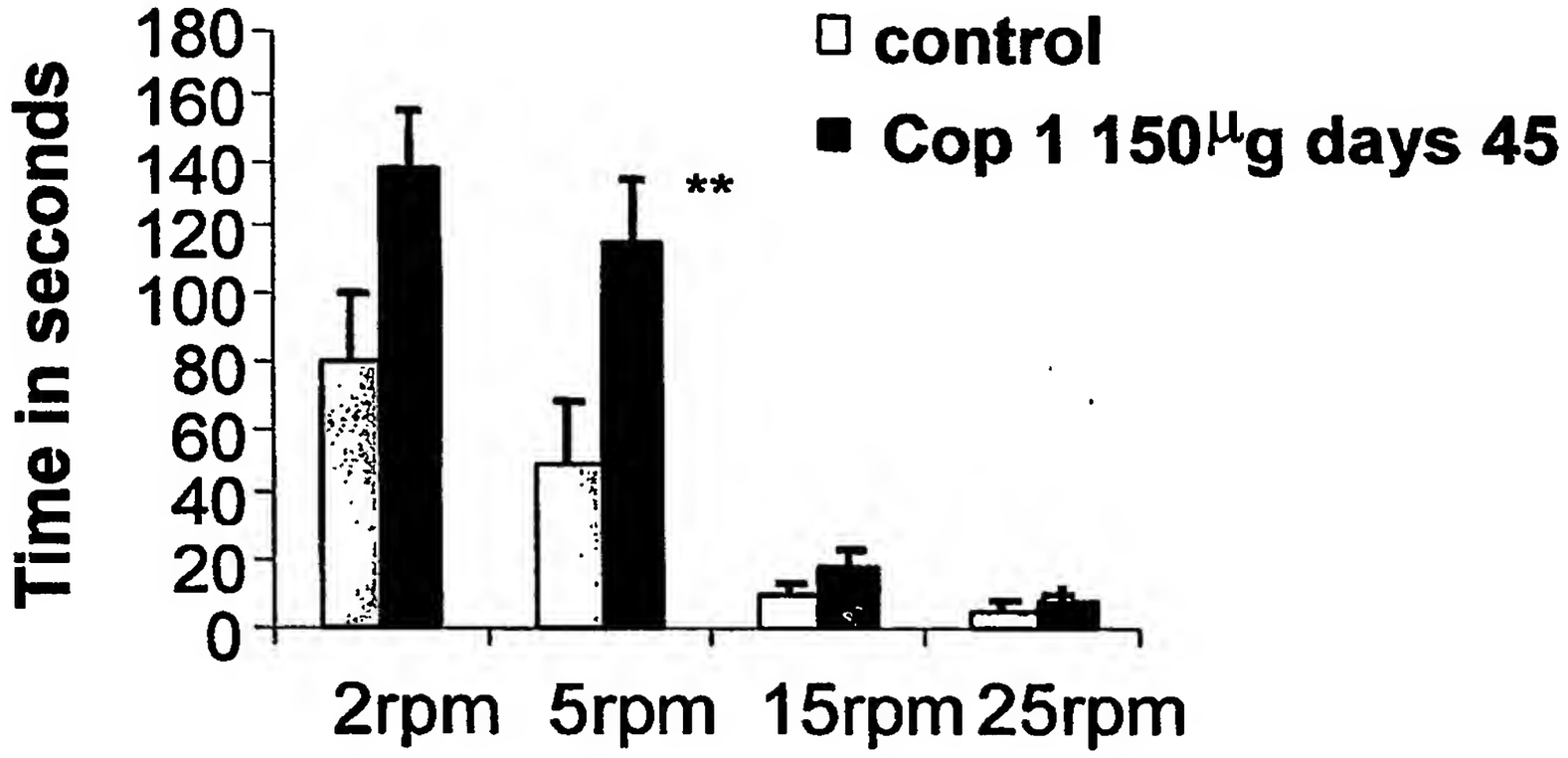
Time in seconds
180
160
140
120
100
80
60
40
20
0
control
Cop 1 150µg days 45
**
2rpm
5rpm
15rpm
25rpm

Fig. 9